PERTIMBANGAN PEMAKAIAN ANTIBIOTIK PADA SEPSIS NEONATAL

Dr. Ariantana, Sp.A

RSIA Limijati

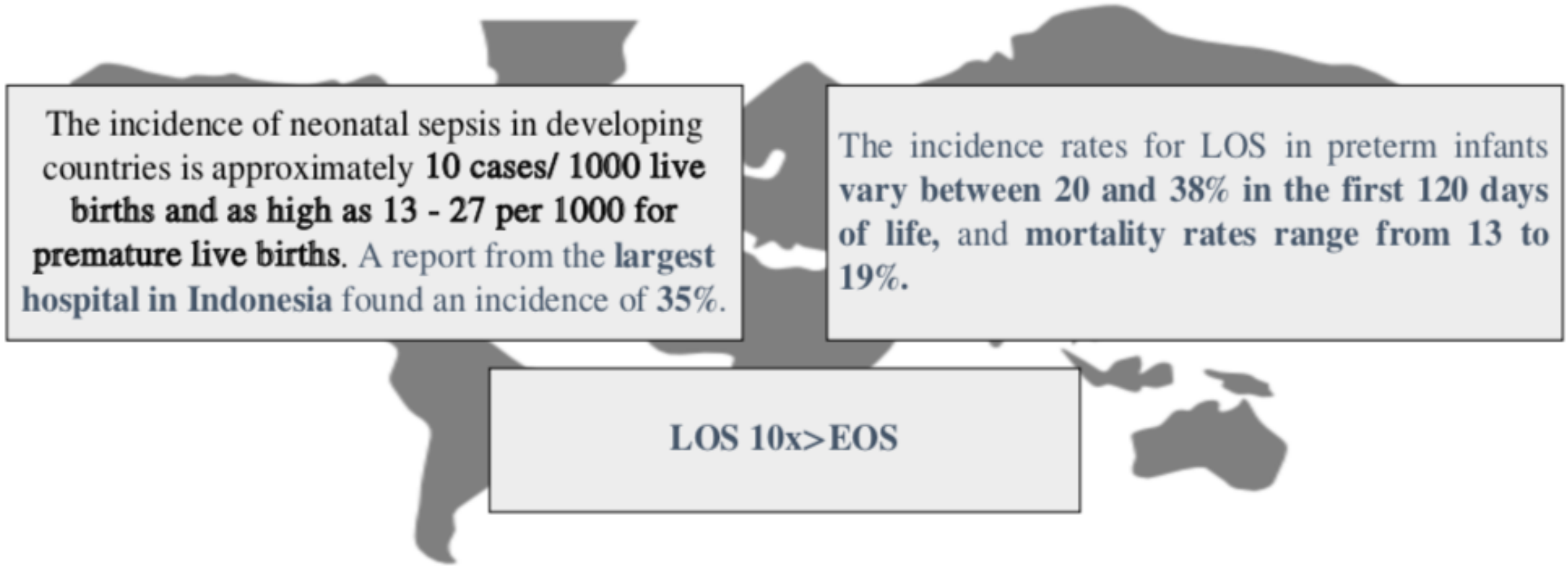
29-30 Mei 2021

INTRODUCTION

- ✓ Neonatal sepsis is a global challenge causing **high morbidity and mortality among newborns**
- ✓ **Late-onset sepsis** (LOS) in preterm infants is a leading cause of mortality and morbidity
- ✓ **Timely recognition and initiation of antibiotics** are important factors for improved outcomes
- ✓ **Antimicrobial therapy in most developing countries are mainly empirical** due to a relative lack of appropriate laboratory facilities for culture and sensitivity of bacteria in several health facilities
- ✓ **Antimicrobial resistance** become a major concern

Alebachew Woldu M.. Pediatr Ther. 2014;04(04).

EPIDEMIOLOGY



The incidence of neonatal sepsis in developing countries is approximately **10 cases/ 1000 live births and as high as 13 - 27 per 1000 for premature live births**. A report from the **largest hospital in Indonesia** found an incidence of **35%**.

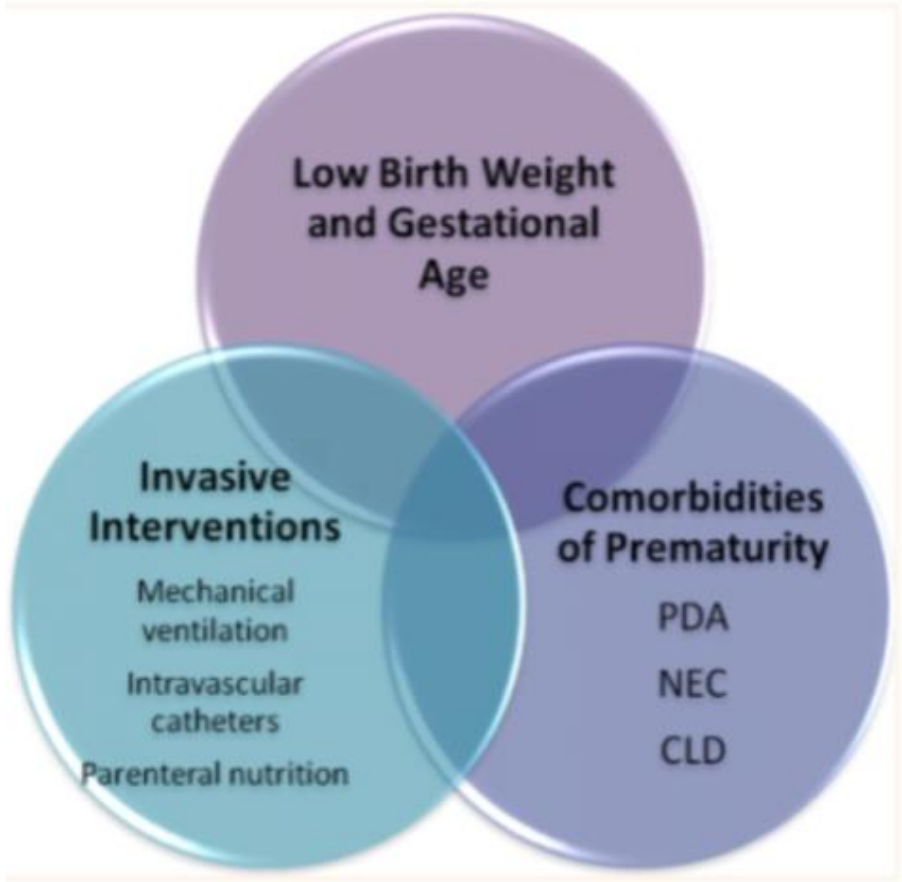
The incidence rates for LOS in preterm infants **vary between 20 and 38% in the first 120 days of life,** and **mortality rates range from 13 to 19%.**

LOS 10x>EOS

El Manouni El Hassani S, Berkhout DJC, Niemarkt HJ, Mann S, De Boode WP, Cossey V, et al. Risk factors for late-onset sepsis in preterm infants: A multicenter case-control study. Neonatology. 2019;116(1):42–51.

FAKTOR YANG BERKONTRIBUSI

Factors contributing to increased risk of LONS in premature infants:
(*Adapted from: Neoreviews 2012;13;e94.*)



Preterm neonates are at higher risk for sepsis/infection than term neonates.

The increased susceptibility for infections seen in preterm neonates is mainly due to :

Deficient immune system, mainly due to decreased IgG antibodies and incompetent opsonization and complement activation.

Comprised innate immune system, caused primarily by the immature epithelial barrier.

The increased need for invasive devices (vascular access, endotracheal tube, feeding tubes and urinary tract catheters) due to associated severe illnesses.

Singh M, Alsaleem M, Gray CP. Neonatal Sepsis. [Updated 2020 Sep 4]. In: StatPearls [Internet]. Treasure Island (FL. Available from:https://www.ncbi.nlm.nih.gov/books/NBK531478/

TANTANGAN

CHALLENGES IN THE DIAGNOSIS OF NEONATAL SEPSIS

- ✓ The clinical diagnosis of infection in a neonate is **unreliable and that excessive**
- ✓ Many early signs of infection in neonates are **nonspecific and may also be simply associated with prematurity or the transition to extrauterine life**
- ✓ **Unnecessary empiric antimicrobial** therapy for the treatment of suspected sepsis can promote antimicrobial resistance
- ✓ **There is a heightened need for an accurate and sensitive diagnostic tool** to confirm the diagnosis of neonatal sepsis

Iroh Tam PY, Bendel CM. Diagnostics for neonatal sepsis: Current approaches and future directions. Pediatr Res [Internet]. 2017;82(4):574–83. Available from: http://dx.doi.org/10.1038/pr.2017.134

DEFINISI

DEFINITION

The incidence of LOS has **increased in parallel with the improved survival of premature infants**, especially in those with **very low birth weight** (VLBW), indicating **the role of hospitalisation and life-sustaining medical devices** in the pathogenesis of neonatal LOS.

	Early Onset	**Late Onset**
Neonatal sepsis categorized	At or before 72 hours of life **(<+/- 7 days)**	After 72 hours of life **(> +/- 7 days)**
	Eos reflects transplacental or, more frequently, ascending infections from the maternal genital tract	Associated with the postnatal nosocomial or community environment, with the peak incidence reported to be between the 10th and 22nd day of life

Dong Y, et al. Arch Dis Child Fetal Neonatal Ed 2015;100:F257–F263.

TANDA INFEKSI

- ✓ Community vs hospital associated infections (HAIs)
- ✓ HAIs: CRBSI, HAP, VAP, CAUTI, SSI
- ✓ Multisystemic or focal (such as UTI, abdominal, meningitis, pneumonia, omphalitis, osteomyelitis, septic arthritis, etc)

HAI's di NICU

	Africa	Southeast Asia	South Asia	Latin America, Caribbean	Middle east, central Asia	All developing regions
All gram positives	606 (38·8%)	926 (41·1%)	1857 (31·0%)	533 (41·7%)	148 (37·9%)	4070 (35·5%)
S aureus	224 (14·3%)	181 (8·0%)	1206 (20·2%)	178 (13·9%)	86 (22·1%)	1875 (16·3%)
Coagulase-negative staphylococci	122 (7·8%)	621 (27·5%)	356 (5·9%)	246 (19·2%)	46 (11·8%)	1391 (12·1%)
Group B streptococci	133 (8·5%)	43 (1·9%)	31 (0·5%)	53 (4·1%)	4 (1·0%)	264 (2·3%)
Other streptococci	45 (2·9%)	14 (0·6)	101 (1·7%)	16 (1·3%)	2 (0·5%)	178 (1·6%)
Group D streptococci/enterococci	27 (1·7%)	1 (0·04%)	132 (2·2%)	22 (1·7%)	9 (2·3%)	191 (1·7%)
S pneumoniae	35 (2·2%)	3 (0·1%)	15 (0·3%)	4 (0·5%)	1 (0·3%)	58 (0·5%)
Group A streptococci	3 (0·2%)	3 (0·1%)	6 (0·1%)	8 (0·9%)	..	20 (0·2%)
Listeria spp	7 (0·4%)	..	..	6 (0·5%)	..	13 (0·1%)
Other gram positives	10 (0·6%)	60 (2·7%)	10 (0·2%)	..	..	80 (0·7%)
All gram negatives	938 (60·0%)	1262 (56·0%)	3793 (63·4%)	709 (55·4%)	239 (61·3%)	6941 (60·5%)
Klebsiella spp	441 (28·2%)	435 (19·3%)	1450 (24·2%)	204 (15·9%)	88 (22·6%)	2618 (22·8%)
E coli	155 (9·9%)	108 (4·8%)	984 (16·4%)	116 (9·1%)	40 (10·3%)	1403 (12·2%)
Pseudomonas spp	51 (3·3%)	158 (7·0%)	576 (9·6%)	92 (7·2%)	27 (6·9%)	904 (7·9%)
Acinetobacter spp	4 (0·3%)	290 (12·9%)	251 (4·2%)	26 (2·0%)	5 (1·3%)	576 (5·0%)
Citrobacter spp	42 (2·7%)		54 (0·9%)	11 (1·3%)	3 (0·8%)	110 (1·0%)
Enterobacter spp	66 (4·2%)	105 (4·7%)	287 (4·8%)	153 (12·0 %)	24 (6·2%)	635 (5·5%)
Salmonella spp	24 (1·5%)	2 (0·1%)	51 (0·9%)	14 (1·6%)	5 (1·3%)	96 (0·9%)
Proteus spp	12 (0·8%)	3 (0·1%)	47 (0·8%)	26 (3·0%)	3 (0·8%)	91 (0·8%)
Serratia spp	..	..	1 (0·02%)	14 (1·6%)	13 (3·3%)	28 (0·3%)
N meningitidis	2 (0·1%)	..	..	2 (0·2%)	3 (0·8%)	7 (0·1%)
Haemophilus spp	3 (0·2%)	..	..	7 (0·8%)	2 (0·5%)	12 (0·1%)
Flavobacterium meningosepticum	..	8 (0·4%)	2 (0·03%)	..	..	10 (0·1%)
Other gram negatives	138 (8·8%)	153 (6·8%)	90 (1·5%)	44 (3·4%)	26 (6·7%)	451 (3·9%)
Candida spp	5 (0·3%)	33 (1·5%)	170 (2·8%)	34 (2·7%)	..	242 (2·1%)
Other pathogens	14 (0·9%)	34 (1·5%)	164 (2·7%)	3 (0·6%)	3 (0·8%)	218 (1·9%)
Total	1563	2255	5984	1279	390	11471

Group B Streptoccus (GBS)

How about GBS? Is it real in Indonesia?

GBS colonization was found in **53 (30%) pregnant women** Serotype II was the most common serotype (30%) followed by serotype III (23%), Ia and IV (13% each), VI (8%), Ib and V (6% each), and one non-typeable strain

Antimicrobial agent	Susceptible, n (%)	Intermediate, n (%)	Resistance, n (%)
Erythromycin	43 (81)	0	10 (19)
Clindamycin	41 (77)	1 (2)	11 (21)
Vancomycin	53 (100)	0	0
Penicillin	53 (100)	0	0
Tetracycline	6 (11)	0	47 (89)
Ampicillin	53 (100)	0	0
Levofloxacin	50 (94)	0	3 (6)
Cefotaxime	53 (100)	0	0
Daptomycin	53 (100)	0	0
Linezolid	53 (100)	0	0

Safari, et al. In press

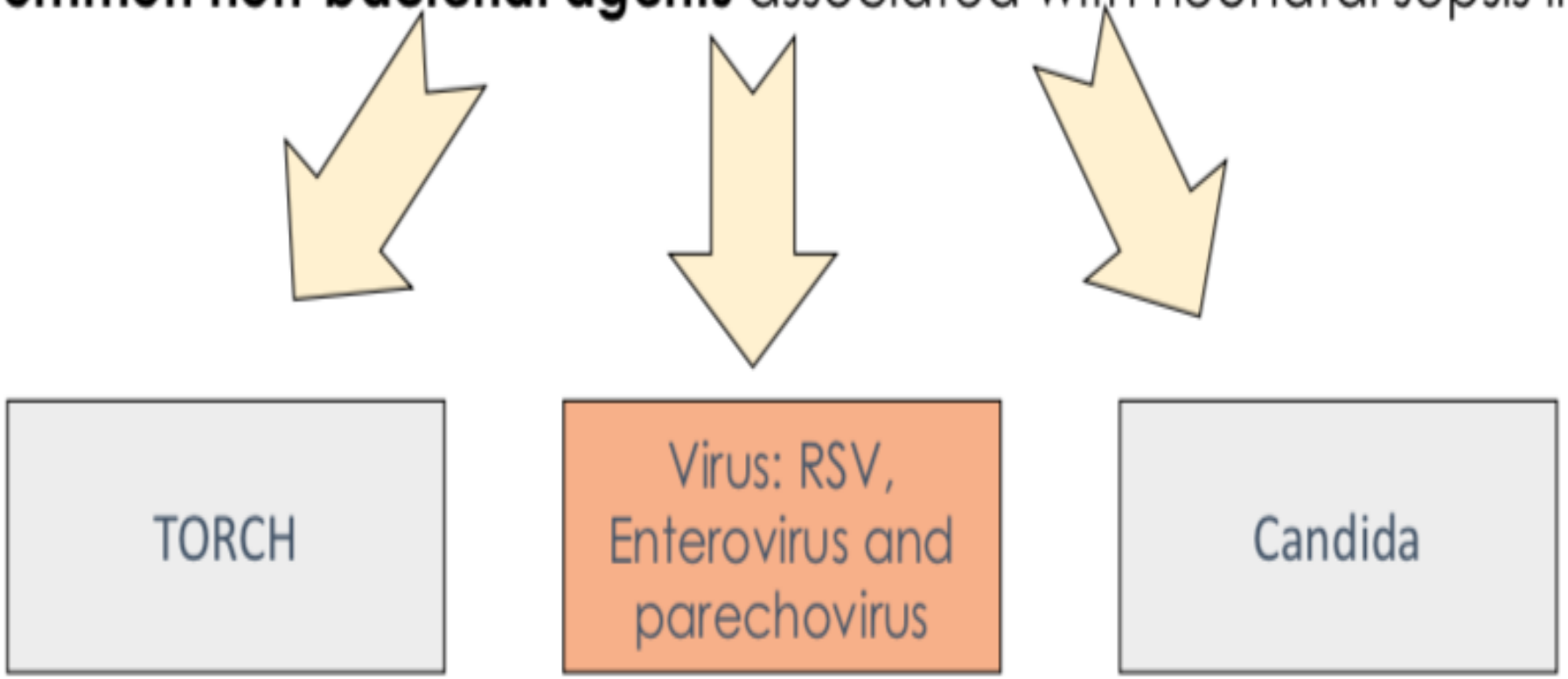
BAKTERIA PENYEBAB

High light bacteria

- Cons:
  - *Staphylococcal epidermidis, S. hominis*
  - Source: hands, lipid, central access
- Enterobacteriaceae:
  - K. pneumoniae, E.coli
  - Source: BF, FM,
- Non fermenter:
  - *Acinetobacter baumanii*: persist in the hospital environment and has the ability to develop resistance to a majority of antimicrobials
  - Pseudomonas
  - Source: environment, water

FAKTOR LAIN LATE ONSET SEPSIS NEONATAL

Common non-bacterial agents associated with neonatal sepsis include:



Armsby C. Official reprint from UpToDate. www.uptodate.com ©2017 UpToDate ® Clinical features, evaluation, and diagnosis of sepsis in term and late preterm infants. 2017;1–23.

PEMERIKSAAN LABORATORIUM

INVESTIGATIONS FOR LATE ONSET NEONATAL SEPSIS

In the case of suspected LONS the infant should have the following investigations:

Blood cultures	Urine microbiology
FBC	CXR +/- AXR
CRP	LP
Respiratory secretions if ventilated or respiratory signs	
Thorough multi-system examination	

- ✓ USG
- ✓ Echo
- ✓ CT-scan
- ✓ Eye check up
- ✓ etc

http://www.lhp.leedsth.nhs.uk/detail.aspx?id=3688#Investigation

PEMERIKSAAN PUNKSI LUMBAL

Lumbal Puncture indications & contraindications

INDICATIONS	CONTRAINDICATIONS
Clinical signs of meningitis	Abnormal clotting
Signs of systemic bacteraemia	Thrombocytopenia
Positive blood culture (except CoNS)	Clinically well
CRP > 30	Definite focus of infection outside the CNS e.g. NEC

http://www.lhp.leedsth.nhs.uk/detail.aspx?id=3688#Investigation

PENDEKATAN DIAGNOSA LATE ONSET SEPSIS NEONATAL

- ✓ **The gold standard** the growth of pathogenic microorganisms in body fluids (blood, urine, cerebrospinal fluid, pleural fluid, peritoneal fluid, joint fluid) that are expected to be sterile
- ✓ This 'gold standard' testing method is time-consuming and may produce false positive results as well as false negative results
- ✓ Timely and accurate diagnosis of LOS is of utmost importance
- ✓ The total number of **neutrophils, immature to total neutrophil ratio** and **CRP** holds promise to **enable a fast and accurate diagnosis of LOS**
- ✓ **Sequential detection of CRP** may help to rule out microbial infections in a timely manner, facilitating an early cessation of antibiotic treatment

Dong Y, et al. Arch Dis Child Fetal Neonatal Ed 2015;100:F257–F263.

MARKER INFLAMASI LAINNYA

C-reactive protein (CRP)	• CRP is increased in inflammatory conditions, **including sepsis** • CRP→ repeat after 24h may be helpful in determining whether infection is a significant likelihood. • If the CRP level remains persistently normal (<1 mg/dL [10 mg/L]), neonatal bacterial sepsis is unlikely
High Sensitivity CRP (hs-CRP)	• High Sensitivity CRP (hs-CRP) > sensitive than conventional CRP • The normal lower value of conventional CRP is accepted as 1 mg/dL, this value is 1 mg/L for hs-CRP • high hs-CRP values were reported to have a significant increase in hs-CRP compared to non-infected newborns • No risk of infection when the hs-CRP value is detected as <0.5 mg/L • Low infection risk when the value is between 0.5–1 mg/L • Moderate infection risk when between 1–3 mg/L • High risk of infection at values >3 mg/L
Procalcitonin	• The PCT level rises rapidly 2-4 hours after exposure to bacterial endotoxin, reaches a peak in 6-8 hours and remains high for 24 hours • The half-life of PCT is 24-30 hours. Due to its rapid rise from the onset of bacterial sepsis, it is considered a better marker for early diagnosis of neonatal sepsis compared to CRP. • Over 2-2.5 ng/ml after postnatal 72 hours should suggest infection

SELAIN KULTUR DARAH….

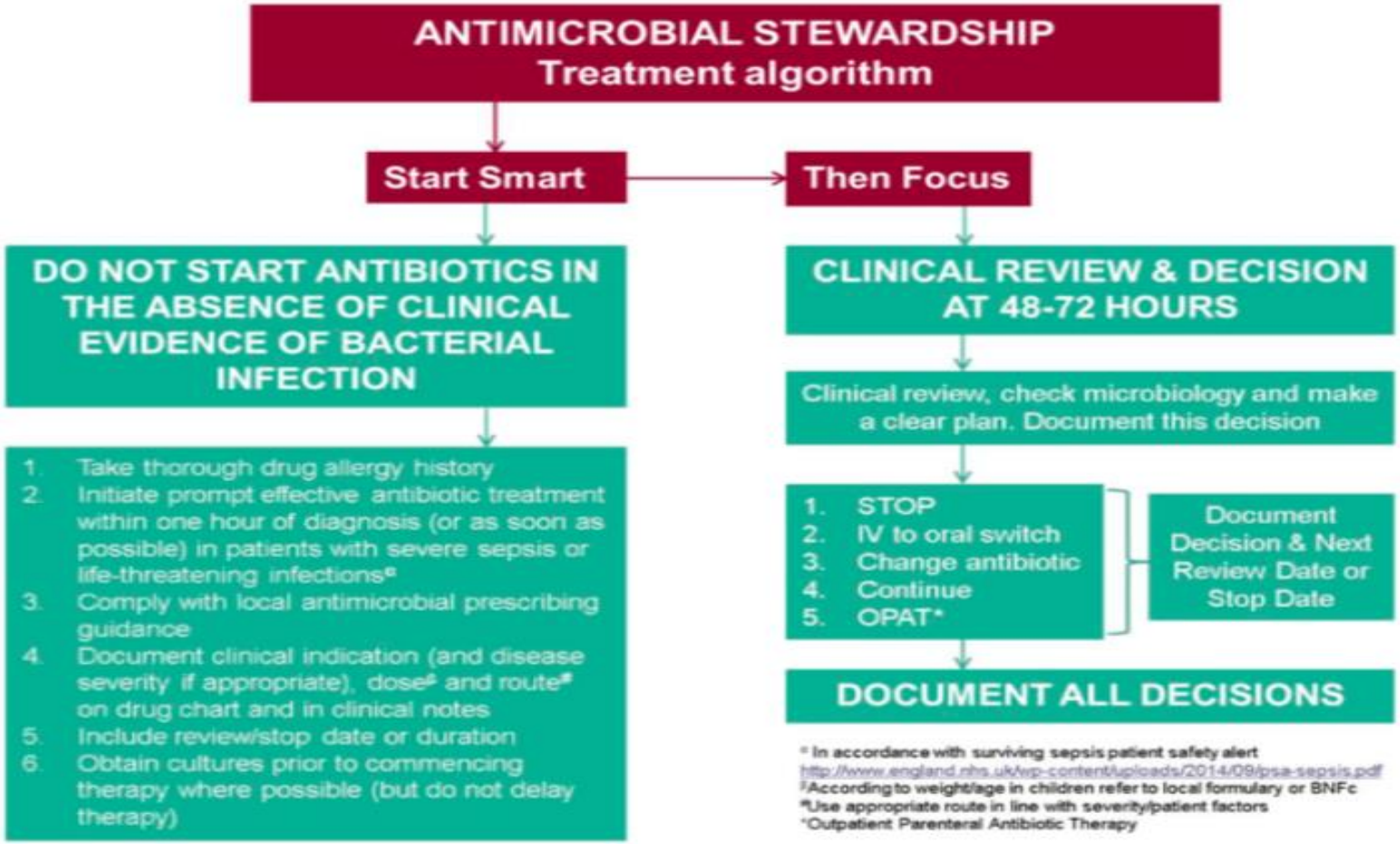
- ✓ **Urine** for microbiological investigation, ideally by suprapubic aspirate (SPA); if this is not possible then catheter or clean catch is appropriate
- ✓ **Tracheal aspirates** obtained immediately after intubation. In infants who has intubated several days → can only be colonization
- ✓ Gram stains from gastric aspirates, cultures from axilla, groin and external ears → limited value, most likely colonization, except for MRSA screening

DIAGNOSIS NEONATAL SEPSIS KULTUR DARAH

Culture proven sepsis	Probable sepsis	Infection unlikely
• **The isolation of pathogenic bacteria** from a blood culture is the gold standard to confirm the diagnosis of neonatal sepsis • A positive blood culture is diagnostic of sepsis when a bacterial pathogen is isolated	• Neonate **has a clinical course** that is concerning for sepsis • But **a pathogen may not be isolated in culture** • **Composite of observational assessment and serial laboratory testing** is typically used to make a diagnosis of probable sepsis	Infants with mild and/or transient symptoms (ex; fever alone or other symptoms that quickly resolve) who **remain well appearing with normal laboratory values and negative cultures at 48 hours** are unlikely to have sepsis.

Armsby C. Official reprint from UpToDate. www.uptodate.com ©2017 UpToDate ® Clinical features, evaluation, and diagnosis of sepsis in term and late preterm infants. 2017;1–23.

KAPAN MULAI ANTIBIOTIKA ?



PEMAKAIAN ANTIBIOTIKA EMPIRIK

1. Try to diagnose the site of infection, do the best educate guess!
2. Collect maximized microbiological work up and use the best/fastest methodologies for microbiological diagnosis
3. Assess severity
4. Assess MDR pathogen's risk factors
5. Decide about the need of combination therapy
6. Use PK/PD concepts such as prolonged or continuous infusion, with TDM whenever possible
7. Use ASP, based on local specificities and data
8. Maintain daily assessment of clinical and supporting exam
9. Promote source control, whenever needed
10. Do not forget non antibiotic adjuvant therapy, whenever indicated

ANTIBIOTICS MANAGEMENT FOR LATE-ONSET NEONATAL SEPSIS

- **Empiric treatment with antibiotics** should be started as soon as sepsis is clinically suspected, even without confirmatory lab data.
- In general, antimicrobial resistance patterns of common bacteria in the neonatal intensive care unit should guide antibiotics '**initial choice'.**
- With LOS, nosocomial coverage should be provided for the hospital-acquired pathogens such as coagulase-negative *Staphylococcus*, *S. aureus*, and *Pseudomonas* species

Singh M, Alsaleem M, Gray CP. Neonatal Sepsis. [Updated 2020 Sep 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK531478/

Bacterial pathogens in neonatal sepsis and focal neonatal infections

	Common pathogens	Some less common pathogens
Late Onset		
Term and late preterm infants (GA ≥ 34 *weeks*)	- GBS - *E. coli* - Additional pathogens seen in the NICU setting- *S. aureus*, CoNS	- *Enterobacter, Listeria, Klebsiella, N. meningitidis*, other enteric and non enteric gram negative bacilli, *Salmonella. pneumoniae*, Viridans streptococci - Additional pathogens seen in the NICU setting- *Citrobacter, Enterococcus, Pseudomonas, Serratia*
Preterm infants (GA <34 weeks)	- CoNS - *S. aureus* - GBS - *E. coli*	- *Citrobacter, Enterobacter, Enterococcus, Listeria, Klebsiella,* other enteric and non-enteric gram negative bacilli, *Pseudomonas, Serratia,* , Viridans streptococci, *Salmonella*

Bacterial pathogens in neonatal sepsis and focal neonatal infections

	Common pathogens	Some less common pathogens
Pathogens based on source of infection		
Meningitis	- GBS - *E. coli* - Other enteric gram negative bacilli	- CoNS, *Enterococcus, Listeria, N. meningitidis,* non- typeable *H. Influenza, S. aureus, S. pneumoniae,* other streptococci (groups A, C, or G, and Viridans streptococci)
Pneumonia	- *GBS*	- *C. trachomatis, Citrobacter, Enterobacter, Group A Streptococcus, Klebsiella, Pseudomonas, S. aureus, S. pneumoniae, Serratia*
Urinary Tract Infection	- *E. coli*	- *Citrobacter, Enterobacter, Enterococcus, Klebsiella, Proteus* - Additional pathogens seen in the NICU setting- CoNS, *S. aureus*
Skin and soft tissue infection	- *S. aureus* - *GBS* - *Group A Streptococcus*	
Vascular catheter- associated infection	- *S. aureus* - CoNS - Gram negative - *Enterococcus*	
Intestinal source/ NEC	- *E. coli* - *Klebsiella* - Other enteric gram negative bacilli - *Clostridium spp.* - *Anaerobes (eg. Bacteroides)*	

Suggested antimicrobial regimens in the management of neonatal sepsis in term and late preterm infants

	Antibiotic regimen
Empiric therapy	
Late onset (≥ 7 *days*): *Admitted from the community*	- Ampicillin AND gentamicin
Late onset (≥ 7 *days*): Hospitalized since birth	
Special circumstances:	
- Suspected meningitis- early onset	- Ampicillin AND gentamicin
- Suspected meningitis – late onset, admitted from the community	- Ampicillin, gentamicin AND cefotaxime
- Suspected meningitis – late onset, hospitalized since birth	- Gentamicin, vancomycin AND cefotaxime
- Suspected pneumonia	- Ampicillin AND gentamicin - Alternatives: Ampicillin AND cefotaxime/ Vancomycin AND cefotaxime/Vancomycin AND gentamicin
- Suspected infection of soft tissue, skin joints, or bones(*S. aureus* is a likely pathogen)	- Vancomycin or vancomycin AND nafcillin
- Suspected intravascular catheter-related infection	- Vancomycin AND gentamycin
- Suspected infection due to organisms found in the GIT (eg. Anaerobic bacteria)	- Ampicillin, gentamicin AND clindamycin - Alternatives: Ampicillin, gentamicin, AND metronidazole / Piperacillin- tazobactam AND gentamicin

ANTIBIOTICS MANAGEMENT FOR LATE-ONSET NEONATAL SEPSIS

- Review clinical progress and microbiology results at **36 hours (48 hours for late** onset sepsis).
  - If cultures negative consider stopping therapy.
  - Continue therapy if cultures positive or sepsis very likely.

- Add metronidazole if suspicion of **anaerobic infection** (e.g. intra-abdominal sepsis, NEC). If abdominal infection/NEC beyond 5 days use amoxicillin in preference to flucloxacillin

- Consider vancomycin for **coagulase negative Staphylococcal sepsis**, especially if infant unwell or central line infection with line staying in.

- Add cefotaxime if **neonatal meningitis**. Consider adding cefotaxime early if neonate has a ventricular reservoir or shunt and after reservoir is tapped by neurosurgical team for a CSF sample.

- Consider cefuroxime or piptazobactam for **ventilator-associated pneumonia.**

https://www.starship.org.nz/guidelines/antibiotics-for-neonatal-sepsis/

Suggested antimicrobial regimens in the management of neonatal sepsis in term and late preterm infants

	Antibiotic regimen
Pathogen specific therapy	
Group B *Streptococcus*	- Penicillin G
E. coli: Ampicillin- sensitive	- Ampicillin
E. coli: Ampicillin- resistant	- Cefotaxime - Alternative: Meropenem
Multidrug- resistant gram negative bacilli (including ESBL- producing organisms)	- Meropenem
Listeria monocytogenes	- Ampicillin AND Gentamicin
Methicillin- susceptible, *S. aureus (*MRSA)	- Nafcillin OR cefazolin
Methicillin- resistant, *S. aureus (*MRSA)	- Vancomycin
Coagulase- negative staphylococci	- Vancomycin

Antibiotics for MDROs

ESBL Enterobactericae: *E. coli, K. pneumoniae*
- Carbapenem, Pip-Taz

AmpC: *Aeromonas sp., Citrobacter sp., Enterobacter sp., Morganella morganii, Serratia marascens; Yersinia enterocolitica; Pseudomonas aeruginosa*
- Cefepime, Carbapenem

MRSA
- BSI: Vancomycin
- Paru: Linezolid, Vancomycin
- Kulit, jaringan lunak: Vancomycin, Teicoplanin

XDR A. baumannii dan Pseudomonas:
- Colistin/Polymixin B + Carbapenem +/- Fosfomycin

KPC (Klebseiella pneumoniae carbapenemase)
- Colistin/Polymixin B + Carbapenem
- Tygecycilin + Carbapenem

Duration of treatment

Infection type	Duration (days) of therapy
Pneumonia	5-7
Septicaemia	7-10
Urinary Tract Infection	7-10
Meningitis	14-21 (depending on organism isolated)
Skin conditions	5
Conjunctivitis	5-7
Oral thrush	7-10

https://www.starship.org.nz/guidelines/antibiotics-for-neonatal-sepsis/

KULTUR (-), NEONATUS MASIH TAMPAK SAKIT

- ✓ Do a source control
  - ✓ Remove central line
  - ✓ Surgical
  - ✓ Infection control: change ventilator, etc
- ✓ Search for other alternative diagnosis
- ✓ Do further microbiology work up
- ✓ Cross check if your dose is correct
- ✓ Know the nature of the disease

Differential diagnosis of neonatal sepsis

Diagnosis	Distinguishing features	Diagnostic tests
Other systemic neonatal infections		
Viral infections:		
Herpes simplex virus	Mucocutaneous vesicles, CSF pleocytosis, elevated CSF protein, thrombocytopenia, hepatitis	Viral culture; HSV PCR
Enteroviruses	Fulminant systemic disease, myocarditis, hepatitis, encephalitis	Viral culture; EV PCR
Parechovirus	Encephalitis/meningitis, rash on palms and soles	HPeV PCR (available through CDC)
Cytomegalovirus	Thrombocytopenia, periventricular intracranial calcifications, microcephaly, sensorineural hearing loss, chorioretinitis	Viral culture; CMV PCR
Influenza viruses	Respiratory symptoms, rhinorrhea, gastrointestinal symptoms	Viral culture; influenza-specific antigen detection or immunofluorescence assay
Respiratory syncytial virus	Respiratory symptoms, rhinorrhea, cough, apnea, pneumonia	Viral culture; RSV-specific antigen detection or immunofluorescence assay
Spirochetal infections – Syphilis	Skeletal abnormalities (osteochondritis and periostitis), pseudoparalysis, persistent rhinitis, maculopapular rash (particularly on palms and soles or in diaper area)	RPR or VDRL
Parasitic infections:		
Congenital malaria	Anemia, splenomegaly, jaundice	Detection of parasitemia on blood smear
Toxoplasmosis	Intracranial calcifications (diffuse), hydrocephalus, chorioretinitis, mononuclear CSF pleocytosis, elevated CSF protein	*Toxoplasma gondii* serology
Fungal infection – Candidiasis	Persistent hyperglycemia, thrombocytopenia, multiorgan failure	Isolation of Candida in blood, urine, or CSF culture

Noninfectious causes of temperature instability in neonates		
Altered environmental temperature	Transient; no other systemic symptoms; resolves with simple nonpharmacologic measures	
Dehydration	Clinical history of poor feeding or fluid losses (eg, vomiting and/or diarrhea)	
Neonatal abstinence syndrome	History of maternal drug use; sweating, sneezing, nasal stuffiness, and yawning	Positive drug screening tests
CNS insult (eg, anoxia or hemorrhage)	History of perinatal asphyxia; focal neurologic findings or seizures	Abnormal neuroimaging studies
Hypothyroidism	Hypotonia, lethargy, hypothermia, large fontanels	Abnormal T4 or TSH level on newborn screen
Congenital adrenal hyperplasia	Ambiguous genitalia (females), adrenal insufficiency and salt-wasting (hyponatremia, hyperkalemia, dehydration)	Abnormal 17a-hydroxyprogesterone level on newborn screen
Noninfectious causes of respiratory and cardiocirculatory symptoms in neonates		
Transient tachypnea of the newborn	Onset of symptoms within two hours after delivery; symptoms usually resolve within 24 hours	CXR findings include increased lung volumes, mild cardiomegaly, prominent vascular markings, fluid in the interlobar fissures, and pleural effusions
Respiratory distress syndrome	Most common in preterm infants; rare in term infants; onset of symptoms within first few hours after delivery, progressively worsens over first 48 hours of life	CXR findings include low lung volume and diffuse reticulogranular ground glass appearance with air bronchograms
Meconium aspiration	History of meconium-stained amniotic fluid; respiratory distress occurs immediately after birth	Initial CXR may show streaky, linear densities; as the disease progresses, the lungs may appear hyperinflated with diffuse patchy densities
Pneumothorax	Asymmetric chest rise, decreased breath sounds on affected side; hypotension (in cases of tension pneumothorax)	CXR will usually detect symptomatic pneumothoraces
Congenital anomalies (including tracheal-esophageal fistula, choanal atresia, and diaphragmatic hernia)	Often occur with other congenital anomalies including VACTERL and CHARGE associations; choanal atresia is characterized by noisy labored breathing while feeding	CDH is often diagnosed by routine antenatal ultrasound screening; postnatal CXR shows herniation of abdominal contents into hemithorax; TEF is diagnosed with upper gastrointestinal series and/or bronchoscopy
Neonatal abstinence syndrome	History of maternal drug use; sweating, sneezing, nasal stuffiness, and yawning	Positive drug screening tests
Cardiac arrhythmias (eg, supraventricular tachycardia)	Abrupt onset and termination of rapid heart rate	Abnormal ECG
Congenital heart disease	Infants with ductal-dependent lesions may initially lack symptoms then develop cyanosis and rapid clinical deterioration as the PDA closes in the first few days of life	Abnormal hyperoxia test; abnormal echocardiography

Noninfectious causes of neurologic symptoms in neonates		
Hypoglycemia	Common in infants who are large for gestational age and/or infants of diabetic mothers	Abnormal blood glucose level
Hypercalcemia	Increased neuromuscular irritability and seizures; associated with prematurity, maternal diabetes, and perinatal asphyxia	Abnormal serum calcium level
Hypermagnesemia	Generalized hypotonia, respiratory depression and apnea; typically results from maternal treatment with magnesium sulfate	Abnormal serum magnesium level
CNS insult (eg, anoxia or hemorrhage)	History of perinatal asphyxia; focal neurologic findings or seizures	Abnormal neuroimaging studies
Congenital CNS malformations (eg, hydrocephalus)	Abnormal head circumference	Abnormal neuroimaging studies
Neonatal abstinence syndrome	History of maternal drug use; sweating, sneezing, nasal stuffiness, and yawning	Positive drug screening tests
Inborn errors of metabolism	Otherwise unexplained acid-base disorders, hyperammonemia, hypoglycemia, hematologic abnormalities, liver dysfunction, and renal disease	Positive newborn screen for inborn errors of metabolism
Pyridoxine deficiency	Refractory seizures	Abnormal plasma pyridoxal-5-phophate level

CSF: cerebral spinal fluid; HSV: herpes simplex virus; PCR: polymerase chain reaction; EV: enterovirus; HPeV: human parechovirus; CMV: cytomegalovirus; RSV: respiratory syncytial virus; RPR: rapid plasma reagin; VDRL: venereal disease research laboratory; CNS: central nervous system; T4: thyroxine; TSH: thyrotropin; CXR: chest radiograph; CDH: congenital diaphragmatic hernia; VACTERL: malformations of the vertebrae, anus, cardiac structures, trachea, esophagus, renal system, and limbs; CHARGE: coloboma of the iris or choroid, heart defect, atresia of the choanae, retarded growth and development, genitourinary abnormalities, and ear defects; TEF: tracheoesophageal fistula; ECG: electrocardiogram; PDA: patent ductus arteriosus.

Adapted from: Nizet V, Klein JO. Bacterial sepsis and meningitis. In: Infectious diseases of the fetus and newborn infant, 7th ed, Remington JS, et al (Eds), Elsevier Saunders, Philadelphia 2010.

TERIMA KASIH....